A Paradigm for the Control of Influenza

Edward B. Lewin
Bethesda, Maryland

(See the article by Glezen et al, on pages 1626–1633.)

In this issue of the Journal, Glezen et al [1] have produced the latest in a series of descriptions of an innovative approach to the control of influenza [2–10]. Dr Glezen and colleagues at Baylor College of Medicine have long been advocates of the concept that the epidemiology of influenza is the most important element in the control of this disease [11, 12].

The study by Glezen and colleagues investigates the effectiveness of immunizing 47.5% of elementary-school children 5–11 years old in 25 public schools and 3 parochial schools in which 1 dose of live attenuated influenza vaccine (LAIV) was administered (intervention group), relative to a comparable community in which vaccine (LAIV or trivalent inactivated vaccine [TIV]) was administered in an off-protocol manner. A significant degree of herd protection (reduction in the number of medically attended acute respiratory illness [MAARI]) was seen in all age groups except 12–17-year-olds, with risk ratios for all age groups >18 years old being lower even than that for the target group of 5–11-year-olds. This occurred despite there being an excess of persons >75 years old in the intervention community. Furthermore, LAIV was 1.7 times more effective in the prevention of proven influenza virus infection in the target group than among those who received TIV and was 6 times more effective than among those who did not receive vaccine.

EPIDEMIOLOGY OF INFLUENZA

Preschool and school-age children are the major disseminators of influenza [11, 12]. They have the highest age-specific attack rates for influenza [12], are less likely to observe cough and sneeze precautions, and are in close proximity to each other and family members. Furthermore, they excrete influenza A virus longer before becoming ill (6 days vs 1 day) and after illness appears (14 days vs 4.5 days), compared with adults [13]. They are centrifugal spreaders to family members, other children, and individuals in the community, including those at high risk [14].

Serious morbidity from influenza is increasing [15], and the negative effect on human life and the economy (~$87 billion per year) is considerable [16]. Previous efforts to control influenza have concentrated on immunizing populations—for example, elderly persons, those medically at risk, and young children [17–20]. This approach has fallen far short of the targets determined by the Healthy People 2010 initiative [20–23]. One of the at-risk groups that has been demonstrated to be at particularly high risk of H1N1/09 infection—pregnant women—has been underimmunized historically. In one study conducted during the 2007–2008 influenza season, only 24% of pregnant women were immunized, the most common reason given being “MD did not mention” [24]. Historically, the group at highest risk is individuals >65 years old, who frequently exhibit immune senescence [25]. Simonsen et al [26] reported no significant effect of influenza vaccine on seasonal mortality among elderly persons. Furthermore, despite an increase in the vaccination rate among individuals >65 years old between 1989 and 1997, mortality and hospitalization rates continued to increase [27], suggesting that administering vaccine to this group is not very effective. This notion is supported by the work of Jackson et al [28, 29], who observed that those who take the vaccine are in better health and are more mobile; therefore, they are more able to receive the vaccine than their sicker counterparts. This has led to an overestimation of the effectiveness of influenza vaccine in this highest-risk age group and may, in part, account for the observation of increasing morbidity and mortality among elderly persons in the face of increasing vaccine use.

Thus, the risk-based approach has not resulted in control of epidemic influenza, nor has it been effective in preventing serious morbidity and mortality.

HERD IMMUNITY

Herd immunity (protection) is defined as vaccinating one group to reduce the ex-
posure of another [30]. More precisely, it describes a type of immunity that occurs when vaccination of a part of the population (the herd) provides protection to unimmunized individuals [31]. The theory is that, for diseases passed from person to person, it is more difficult to maintain the infection when large numbers are immune. The more individuals who are immune, the lower the chance that a susceptible person will come into contact with an infectious person. Herd immunity is not achieved when an effective vaccine is not available or when vaccines are rejected by a segment of the population. Epidemics of pertussis [32], measles [33], and mumps [34] and a resurgence of cases of *Haemophilus influenza* type b infection [35] have appeared in regions in which immunization has been refused.

Herd immunity has been demonstrated for viral diseases (eg, rubella, measles, and mumps), as well as for diseases caused by bacteria (eg, *H. influenza* type b, and *Streptococcus pneumoniae*). In the case of rubella, widespread immunization in the United States has resulted in a reduction of the frequency of congenital rubella syndrome from 823 cases per year to 1 [36]. By comparison, in the >50% of countries in which rubella immunization is not routinely administered, >100,000 cases of congenital rubella syndrome occur [37].

Considerable evidence indicates that herd immunity is operative in the control of influenza as well. In Tecumseh, Michigan, >85% of 3159 schoolchildren were given TIV over 4 days and compared to a similar population in the neighboring community of Adrian, where vaccine was not administered. Three times more influenza-like illness occurred among people of all ages in Adrian than in Tecumseh, demonstrating that immunizing schoolchildren in a community significantly protects the population at large in that community [38]. In 1962, Japanese authorities mandated that all schoolchildren 5–15 years old receive TIV. That practice rapidly and significantly decreased the number of excess deaths attributable to pneumonia and influenza, predominantly among elderly persons. It was estimated that up to 49,000 deaths were prevented annually and that 1 death was prevented by immunizing 420 schoolchildren. In 1986, parents were allowed to refuse vaccination, and the excess death rate rose [39]. In the Temple-Belton area of Texas, schoolchildren in 2 counties were immunized with LAIV and compared with unimmunized children in 3 counties for the incidence of MAARI among adults >35 years old; even with a vaccine uptake rate of only 20%–25%, indirect protection of 8%–18% of the adults studied occurred [40]. In Russia, Rudenko et al [41] gave either LAIV or TIV to 35%–65% of schoolchildren 7–14 years old. Respiratory illness rates among adults on staff and unimmunized children were inversely related to coverage rates in the immunized children, suggesting that herd immunity occurred. In a day care setting in San Diego, 149 children 24–60 months old and their families received either TIV or hepatitis A vaccine; despite the <45% efficacy of the seasonal TIV used, there was an 80% reduction in the frequency of febrile respiratory illness and a 72% decrease in absenteeism for the school-age contacts [42]. In another Russian study, 1 dose of TIV was given to school-age children 3–17 years old (coverage, 57%–72%) in one community (immunized) and none was given to another (comparison). Both communities contained >400,000 people. In the comparison community, the rate of influenza-like illness in adults >60 years old was 3.4 times higher [43]. In the Maryland SchoolMist Study, LAIV was administered to 40% of a targeted elementary school, and 2 other nonimmunized schools served as controls. Significantly fewer child and adult medical visits for episodes of febrile respiratory illness, fewer over-the-counter medications purchased, and fewer days of absenteeism were noted among both children and adult members of families in which children were immunized [44]. In 2000, Ontario, Canada, initiated a universal influenza immunization program for individuals >6 months old [45]. Other provinces used targeted vaccination, and Ontario’s vaccination rate increased 20%, compared with 11% in other provinces (P = .004). Mortality rates for influenza and influenza-associated health care use decreased significantly more in Ontario than in the other provinces [36]. Finally, Weycker et al [46], using a stochastic epidemic model of influenza transmission, clinical illness, and economic costs, estimated the benefits of routinely vaccinating children >6 months old against influenza. They predicted that immunizing 20% of this population would result in a reduction in the number of influenza cases by 46% and that 80% coverage would reduce the number of cases by 91%. Similar concurrent reductions were estimated to occur for influenza-related mortality and economic costs. Thus, significant evidence exists for the operative workings of herd immunity for influenza.

## SCHOOL IMMUNIZATION

In 1954, the “biggest public health experiment ever” was conducted in schools under the supervision of the National Foundation for Infantile Paralysis. The scene was vividly described by David Oshinsky in his book *Polio: An American Story* [47]. Hepatitis B vaccine [48] and measles, mumps, and rubella boosters [49] have also been administered successfully in the school setting. Since 2003, LAIV has been administered to 780,000 children in the United States in the school setting (data on file, Medimmune, Inc.). It has been demonstrated that this vaccine has greater efficacy than TIV in children [50, 51], with its efficacy lasting through 12 months for most strains and into the second season without revaccination for ~50% of strains [45, 52]. In one study, LAIV was found to be safe without an increased risk of asthma events for all children 18 months to 18 years old [53], as was also demonstrated in the present study by Glezen [1]. It also has significant activity against mismatched strains [1]. Finally, LAIV is easy to ad-
References


